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Case Report: Fatal Staphylococcal Infection following Classic Dengue Fever

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Abstract. Dengue represents an important public health issue in many tropical areas, leading to high morbidity and the employment of substantial health resources. Even though the number of fatalities related to dengue is unknown, several reports warn about the potential occurrence of severe infections and even death. The clinical spectrum of dengue is highly variable, ranging from a mild flu-like syndrome to severe disease, with shock and hemorrhage. The occurrence of bacterial superinfection, or coinfection, in patients with dengue has been noted by some authors, but the available information comes from anecdotic reports. In this study, we show the clinical and anatomopathological data of a patient infected with dengue, who subsequently died of acute multi-organic failure related to *Staphylococcus aureus* infection. The autopsy revealed a severe disseminated staphylococcal disease and confirmed dengue infection.

INTRODUCTION

Dengue represents the commonest arboviral disease transmitted globally,[1] transmitted to humans by an arthropod vector (*Aedes aegypti*). Dengue virus, an RNA + sense virus, member of the flavivirus group in the family *Flaviviridae*, presents four antigenically distinct virus serotypes, DEN–1, DEN –2, DEN –3, and DEN –4. The clinical manifestations of dengue range from a mild flu-like syndrome to a serious hemorrhagic fever usually associated with shock. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), particularly, are the most severe clinical forms of dengue infection, with a mortality rate around 5%.[2,3] In the past few years, there has been a very significant increase of dengue fever infection in tropical areas such as Asia, Africa, and Latin America, including Brazil,[4,5] which constitutes a tremendous public health challenge. It is estimated that 2 to 5 billion people are under risk of acquiring the infection worldwide, with 50 to 100 million infections reported annually, and approximately 500,000 hospital admissions. Death numbers associated with dengue are difficult to estimate.[3,6]

The spread of dengue fever disease worldwide allowed the observation of a correspondingly higher number of patients with atypical clinical presentations.[1] According to some authors, many of these unusual presentations of dengue might be linked to concurrent infections, caused by fungi,[7–9] protozoa,[10] or bacteria.[11]

We report herein the case of a patient initially diagnosed with classical dengue fever, who subsequently developed a fatal septic shock caused by *Staphylococcus aureus*. The pathological findings confirmed bacterial and viral co-infection. Bacteremia in the course of dengue infection is rarely described in medical literature, Hongsiriwon,[12] Pancharoen,[11] Lee,[13] Sudjana and others,[14] Charrel and others,[15] and Chai and others.[16]

CASE REPORT

RMS, a 14-year-old Brazilian male, a healthy student and athlete, presented on January 2, 2008 with acute fever, headache, myalgia, arthralgia, prostration, and maculopapular rash. He had a presumptive diagnosis of classic dengue fever, and recovered completely in a few days with antipyretics and analgesics. One month later (February 3), the patient presented a new episode of high grade fever (39.2°C), accompanied by prostration and myalgia, which became worse on the following day. Moreover, he also showed discrete mental confusion, headache, visual turbidity, sore joints, and disseminated petechial rash, predominantly distributed in the trunk and upper limbs, including palms and soles.

The patient was admitted to the hospital and treated with antipyretics, 0.9% NaCl infusion and intramuscular 1,200,000 IU benzatin penicillin, with slight clinical improvement overnight. Nevertheless, the next day (February 4), a significant clinical worsening was observed, with deteriorating mental condition, psychomotor agitation, respiratory distress, arterial hypotension, and emergence of subungual hemorrhages.

Laboratory exams were obtained, the results of which were as follows: hemoglobin 18.0 g/dL, hematocrit 54%, leukocyte count 2.100/mm^3 (band neutrophils 5%, segmented neutrophils 71%, monocytes 10%, lymphocytes 12%), and platelets 74.000 mm^3; international normalized ratio (INR) 1.97, fibrinogen 213 mg/dL; C-reactive protein 363 mg/dL; blood urea nitrogen (BUN) 67 mg/dL; total creatine kinase (CK) 28.170 U/L, aspartate aminotransferase (AST) 696 U/L, alanine aminotransferase (ALT) 156 U/L, and creatinine 2.23 mg/dL. Arterial gasometry results were pH 7.215, $paCO_2$ 24.7 mmHg; paO_2 145.9 mmHg; HCO_3 9.6 mmHg; BE 17 mmol/L and Lactic Acid 9.5 mmol/L.

The patient was transferred to the intensive care unit, and promptly received ceftriaxone (2 g IV), 6,000 mL of 0.9% NaCl infusion and vasopressors (norepinephrine). The patient had multi-organ dysfunction, with renal failure, coagulopathy, respiratory failure, and refractory shock, dying on February 5, despite the intensive therapeutic efforts. A lumbar puncture was rendered impossible because of the clotting disorder. There were no micro-organisms identified in blood cultures. Dengue's serology was positive by two different methods, immunochromatography, immunoglobulin M (IgM)/IgG, and M antibody capture-enzyme-linked immunosorbent assay (MAC-ELISA) dengue reaction, serotypes 1, 2, 3. Polymerase chain reaction (PCR) of the blood-serum was negative for dengue virus.

Under authorization of the relatives, and because of the peculiar severity of this case, an autopsy was obtained, which

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showed *S. aureus* sepsis, multisystemic septic embolization, and massive tissue colonization, notably in the heart, brain, and kidneys. An acute fibrin-purulent bacterial pancarditis was observed, with 550 mL of pericardial fluid, with focal liquefactive necrosis with an abscess formation and presence of bacterial colonies in both the myocardium and endocardium, predominating in the left ventricle (Figure 1). In addition, there was acute multifocal necrotizing and purulent meningoencephalitis, in correspondence with mycotic aneurysms in branches of the brain's leptomenigeal small arteries and numerous brain abscesses in the cortex, white matter, midbrain, pons, and cerebellum (Figure 2), and massive intraventricular hemorrhage with diffuse and severe cerebral edema. There was also severe acute pyelonephritis constituted by cortical microabcesses, especially in correspondence with septic emboli. Septic emboli were found in several other organs, such as in the liver, spleen, intestines, and thyroid. In the lungs, there was diffuse alveolar damage, with accentuated alveolar edema throughout the pulmonary parenchyma, formation of hyaline membranes, and areas of subpleural hemorrhage; there was a multifocal and interstitial mononuclear inflammatory exsudate, but no signs of bacterial emboli. Bilateral hydrothorax—1,000 mL at the right and 800 mL at the left—was found. The immunohistochemical analysis for dengue virus was strongly positive in sections of the spleen, liver, and brain (Figure 2). In swabs obtained from the meninges, and from all serosal fluids, oxacillin-sensitive *S. aureus* was isolated.

DISCUSSION

Dengue fever is defined as probable in patients presenting with sudden fever with two or more of the following clinical findings (headache, retro-orbital pain, myalgia, arthralgia, rashes, bleeding, and leukopenia), in conjunction with positive serology or the presence of confirmed cases in the same time and regional location. The infection is confirmed through 1) isolation of the virus from peripheral blood or from tissue samples (biopsy or autopsy); 2) detection of viral antigens in the serum or cerebrospinal fluid (CSF); 3) positive serology with IgM (acute infection) and/or IgG reactivity to one or more dengue viral antigens; or 4) detection of viral genomic sequence from autopsy tissues, CSF, or serum by PCR.[1] To show viral antigens one may perform immunohistochemical, immunofluorescence, or enzyme immune assay (EIA). Dengue virus infection may result in a widescale of clinical manifestations, ranging from a mild influenza-simile syndrome to severe life-threatening forms, such as DHF and DSS. Between the extremes, a broad spectrum of clinical presentations may occur, and some patients present subclinical infection.

The IgM is generally detected up to 3 months, but it may persist as detectable until 1 year. The IgG is often present after the fifth day of infection. The patient exams showed negative PCR for dengue virus of blood serum indicating that the virus was not circulating in the blood stream, which would have been the case if the patient had been in the acute phase of the disease. Nevertheless, the immunohistochemical reaction revealed positive results; at the Evandro Chagas pathology experience, detection of virus particles was noticed by electron microscopy and immunohistochemical reaction even after 30 days of the primary infection.

Dengue hemorrhagic fever and dengue shock syndrome are characterized by rapid capillary plasma leakage followed by thrombocytopenia, clotting disorders, and hepatic changes showed by the increase of aspartate transaminase and glutamate transaminase. The endothelium is the main target of the imunopathological mechanisms in dengue. Therefore, the endothelial barrier aggression by dengue virus induces endothelial cell apoptosis, because of a possible mechanism

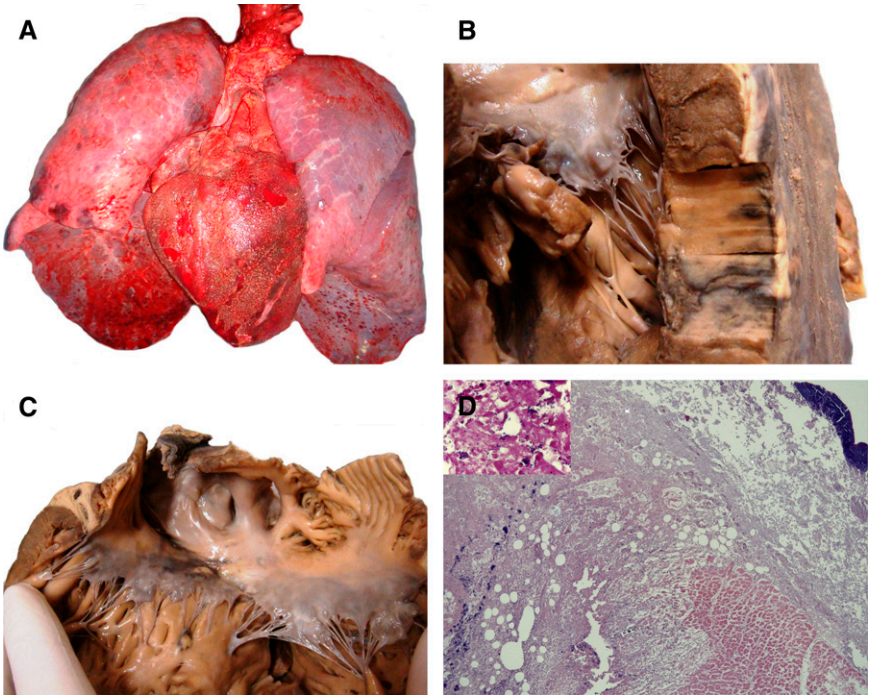

FIGURE 1. Fibrinous pericarditis with myocardial and endocardial liquefactive necrosis and abscess formation. (**A**) Lungs and heart in monoblock, showing fibrinous deposits on the epicardium. (**B**) Detail showing an area of liquefactive necrosis spanning epicardium to endocardium. (**C**) Area of subendocardial necrosis in the left ventricle (asterisks). (**D**) Area of myocardial liquefactive necrosis with bacterial colonies. Detail showing the Gram-positive bacteria. This figure appears in color at www.ajtmh.org.

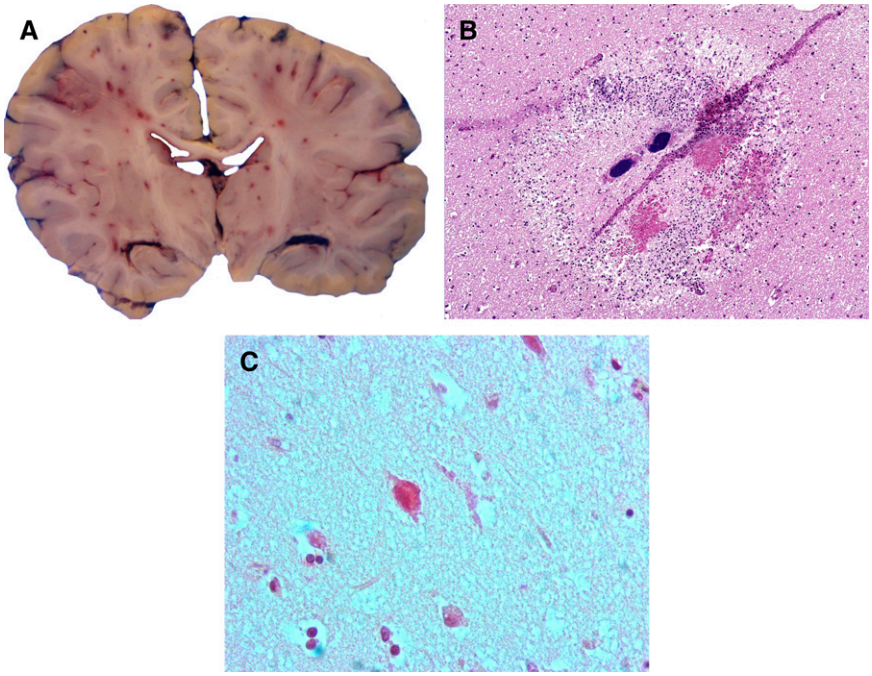

FIGURE 2. Multifocal necrotizing encephalitis (**A**) numerous brain abscesses. (**B**) Brain with area of liquefactive necrosis, hemorrhage, and bacterial colonies. (**C**) Positive imunohistochemichal reaction for dengue viral antigens in the brain. This figure appears in color at www.ajtmh.org.

for the rupture of skin integrity and consequent infection facilitation. Eczema is an instance of this.[3]

Some micro-organisms have been identified as occurring simultaneously with dengue virus infection. Among them, one can mention *Escherichia coli*, *Salmonella* sp., *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Shigella sonnei*, *Klebsiella pneumonia*, *Klebisella ozaenae*, *Enterococcus faecalis*, *Moraxella lacunata*, *Staphylococcus aureus*, *Rosemonas* sp., *Haemophilus influenza*, *Candida tropicalis*, and *herpes viruses*.[7–16] One of the mechanisms proposed to explain these co-infections would involve lesion of the digestive epithelial barrier, possibly through endothelial damage or intestinal hemorrhage, rendering it possible for pathogens found there to enter the circulation. Actually, there seems to be a predominance of intestinal flora micro-organisms in such cases.[13] Additionally, physiopathological changes of the vascular and hemostatic system observed in some organs or systems may predispose to complicating infections. Finally, the occurrence of bacterial infection superimposed on the dengue virus infection might occur as a mere temporal coincidence or, more likely, have the ways paved by a supposed immunosuppression caused by the virus.

Some viruses, such as the measles virus, influenza, Parvovirus B19, and cytomegalovirus are known to induce transient immunosuppression *in vitro* and *in vivo*.[17] Chai and others[16] observed that, instead of being related to a bacterial hypervirulence, cases of *S. aureus* infection occurring in patients with dengue result mostly of an increased immune susceptibility determined by the dengue virus. Among 774 patients presenting with DHF/DSS, Lee and others[13] observed that 5.5% of the patients also showed bacteremia. The authors warn that the occurrence of co-infection by dengue and bacteria has been underestimated, and that few reports have been published so far.

Heart involvement is infrequent in dengue infection, even though, atrial-ventricular blocks, atrial fibrillation, and other arrhythmias have been documented.[18] At first, the patient described in this report did not have any cardiac abnormalities. At the onset of the bacterial sepsis, the patient had only discrete abnormalities in the electrocardiogram, such as sinus tachycardia, despite the anatomopathological diagnosis of bacterial fibrinous pericarditis extending to myocardium. The echocardiogram showed diffuse hypokinesia of the left ventricle walls with loss of its global function (EF= 45%); pericardial effusion and subendocardial staphylococcal microabscesses were also observed during the autopsy. Actually, the heart was the most affected organ, and likely the primary focus of the bacterial sepsis. Remarkably, no valvar lesions were observed.

The patient showed no neurological abnormalities in the acute phase of dengue fever. However, the patient had relevant neurological symptoms, which were probably caused by the septic syndrome rather than dengue infection. At the autopsy, there was serious meningoencephalitis, with multiple bacterial abscesses. Presence of dengue virus infection was also demonstrated by immunohistochemistry. Neurologic disorders have been increasingly reported in patients with dengue. There may be disturbance of consciousness, seizures, coma, polyneuropathies, Guillain-Barré syndrome, and transverse myelitis [Lum 1996,[19] Leão 2002.[20] Solomon and others[21] found dengue viruses in 4.2% of the patients with CNS infections; these findings indicate that the virus can cross the hematoencephalic barrier and infect the brain by microvascular or frank hemorrhage and its intrinsic neurotropism. Alternatively, the virus may be transported to the CNS by infected macrophages, with consequent dengue-induced encephalitis. Some complications such as hypotension, cerebral edema, hyponatremia, and fulminant hepatic failure might also be implicated as possible causes of dengue encephalopathy. Dengue encephalitis is caused mostly by serotypes 2 and 3, and the final diagnosis requires immunohistochemical confirmation.[21]

It was not clear whether the permanence of viral antigens in tissues, as demonstrated by immunohistochemistry, had any impact on the serious septic syndrome that the patient developed, or, rather, the sepsis was related to a state of immunosuppression inherent to the recovery phase of dengue fever, which appears to be more likely.

All of the features of the bacterial superinfection were demonstrated solely at autopsy and would never have been disclosed if the procedure had not been performed.

CONCLUSION

Clinicians should be very vigilant to unusual manifestations of dengue fever, which may signalize a concomitant infection by other microorganisms, mainly bacteria. Case studies like the one reported here may contribute to increased awareness of these associated life-threatening infections.

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